

527 Rec'd PCT 21 NOV 2000

FORM PTO-390
(REV 10-2000)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S SOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

661-50303

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

09/700906

INTERNATIONAL APPLICATION NO.

PCT/EP99/03451

INTERNATIONAL FILING DATE

20 May 1999

PRIORITY DATE CLAIMED

22 May 1998

TITLE OF INVENTION ANTISENSE OLIGONUCLEOTIDES FOR TREATING PROLIFERATING CELLS

APPLICANT(S) FOR DO/EO/US Flad, Hans-Dieter; Bohle, Andreas; Deinert, Irina

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. ☒ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☒ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☒ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A **FIRST** preliminary amendment.
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: Amend claims 4-8, 10 and 13 as follows, prior to calculating claim fees and without prejudice:

Claim 4, line 1, delete "bis 3".
 Claim 5, line 1, delete "bis 4".
 Claim 6, line 1, delete "bis 5".
 Claim 7, line 1, delete "bis 6".
 Claim 8, line 1, delete "bis 7".
 Claim 10, line 1, delete "bis 8".
 Claim 13, line 1, delete "oder 12".

The Claims have been amended to remove multiple dependency only.
 No claims have been amended to overcome prior art.

09/700906

INTERNATIONAL APPLICATION NO
PCT/EP99/03451

526 Rec'd PCT/EP 21 NOV 2000

ATTORNEY'S DOCKET NUMBER
661-50303

CALCULATIONS PTO USE ONLY

17. ☒ The following fees are submitted:**BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :**

Neither international preliminary examination fee (37 CFR 1.482)
nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO
and International Search Report not prepared by the EPO or JPO \$1000.00

International preliminary examination fee (37 CFR 1.482) not paid to
USPTO but International Search Report prepared by the EPO or JPO \$860.00

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but
international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$710.00

International preliminary examination fee paid to USPTO (37 CFR 1.482)
but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00

International preliminary examination fee paid to USPTO (37 CFR 1.482)
and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =

\$ 860

Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30
months from the earliest claimed priority date (37 CFR 1.492(e)).

\$ 130

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	15 - 20 =	0	X \$18.00
Independent claims	3 - 3 =	0	X \$80.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$270.00

\$

TOTAL OF ABOVE CALCULATIONS =

\$ 990

☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above
are reduced by 1/2.

\$

SUBTOTAL =

\$ 990

Processing fee of \$130.00 for furnishing the English translation later than ☐ 20 ☒ 30
months from the earliest claimed priority date (37 CFR 1.492(f)).

\$ 130

TOTAL NATIONAL FEE =

\$ 1,120

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be
accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +

\$

TOTAL FEES ENCLOSED =

\$1,120

Amount to be
refunded:

\$

charged:

\$ 1,120

- a. ☒ A check in the amount of \$ 1,120 to cover the above fees is enclosed.
- b. ☐ Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees.
A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any
overpayment to Deposit Account No. 50-0687. A duplicate copy of this sheet is enclosed.
Under Order No. : 62-661

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Customer No. 20736

SIGNATURE

Jeffrey S. Melcher

NAME

35,950

REGISTRATION NUMBER

November 21, 2000

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) <div style="font-size: 1.5em; font-weight: bold;">09/700906</div>		INTERNATIONAL APPLICATION NO. PCT/EP99/03451		ATTORNEY'S DOCKET NUMBER 661-50303	
--	--	---	--	---------------------------------------	--

17. <input checked="" type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) : Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1000.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$710.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00 <div style="text-align: right; font-weight: bold;">ENTER APPROPRIATE BASIC FEE AMOUNT =</div>	CALCULATIONS PTO USE ONLY																	
	\$ 860																	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	\$ 130																	
<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <th style="width:15%;">CLAIMS</th> <th style="width:20%;">NUMBER FILED</th> <th style="width:20%;">NUMBER EXTRA</th> <th style="width:20%;">RATE</th> </tr> <tr> <td>Total claims</td> <td>15 - 20 =</td> <td>0</td> <td>X \$18.00</td> </tr> <tr> <td>Independent claims</td> <td>3 - 3 =</td> <td>0</td> <td>X \$80.00</td> </tr> <tr> <td colspan="3">MULTIPLE DEPENDENT CLAIM(S) (if applicable)</td> <td>+ \$270.00</td> </tr> </table>	CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	Total claims	15 - 20 =	0	X \$18.00	Independent claims	3 - 3 =	0	X \$80.00	MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$270.00		
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE															
Total claims	15 - 20 =	0	X \$18.00															
Independent claims	3 - 3 =	0	X \$80.00															
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$270.00															
TOTAL OF ABOVE CALCULATIONS =	\$ 990																	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.	\$																	
SUBTOTAL =	\$ 990																	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	\$ 130																	
TOTAL NATIONAL FEE =	\$ 1,120																	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property	\$																	
TOTAL FEES ENCLOSED =	\$ 1,120																	
	Amount to be refunded:	\$																
	charged:	\$ 1,120																

a. ☒ A check in the amount of \$ 1,120 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees.
 A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any
 overpayment to Deposit Account No. 50-0687. A duplicate copy of this sheet is enclosed.
 Under Order No.: 62-661

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Customer No. 20736

SIGNATURE
 Jeffrey S. Melcher
 NAME
 35,950
 REGISTRATION NUMBER

PTO RECEIPT FOR INDICATED ITEMS

Transmittal Letter to US Designated Office Concerning Filing Under 35 USC 371

International Application No.: PCT/EP99/03451

Inventor: Flad

Title: Antisense Oligonucleotides for Treating Proliferating Cells

Attorney Docket No.: 661-50303

Preliminary Amendment

Fee Sheet

Check for \$1,120.

The PTO did not receive the following
listed item(s)

NO Preliminary Amendment

09/700906

Current Due Date: November 22, 2000

527 Rec'd PTO 21 NOV 2000

Certification of Translation

I, Heinz-Peter Muth of UEXKÜLL & STOLBERG, Patent Attorneys in Hamburg, Germany, do hereby certify that I am conversant with the English and German languages and am a competent translator thereof, and I further certify that to the best of my knowledge and belief the foregoing is a true and correct translation made by me of the International Application No. PCT/EP99/03451 filed May 20, 1999 into the English language.

Hamburg, January 5, 2001



Heinz-Peter Muth

Antisense oligonucleotides for treatment of proliferating
cells

The invention relates to oligoribo- and oligodeoxyribonucleotides which are suitable for treating pathological conditions accompanied by an increased cell proliferation.

5 Nucleic acid fragments of which the sequence is complementary to the coding or "sense" strand of DNA or a messenger RNA (mRNA) and which are therefore capable of binding specifically to these complementary target sequences (hybridizing) are called antisense oligonucleotides. Selective influencing of cell processes is
10 possible by this means. Antisense oligonucleotides have found interest as tools in research and as potential agents for antiviral and tumour therapy (E. Uhlmann, A. Peyman, Chemical Reviews, 90 (1990) 544-584; S. Agrawal, TIBTECH 10 (1992) 152-158) and in some cases have already reached the stage of clinical
15 research (M.D. Matteucci, R.W. Wagner, Nature 384 (1996) 20-22).

Ki-67 is a cell protein which is produced in all active phases of the cell cycle (G_1 , S, G_2 and mitosis), but not during the resting phase (G_0). The resting or G_0 phase describes the state
20 in which the dividing activity of the cell is at rest, i.e. the cells have left the active phases of the cell cycle and do not divide. Ki-67 is a human nuclear protein, expression of which is associated strictly with cell proliferation. Specific antibodies against the Ki-67 protein are used in histopathology
25 for determination of the proportion of growing cells in human tumours (J. Gerdes, Seminars in Cancer Biology 1 (1990) 199-206).

It has furthermore been found that proliferation of human IM-9 cells can be inhibited as a function of the concentration by a
30 Ki-67 protein antisense 2'-deoxyoligonucleotide comprising 21

- 3 -

Oligoribo- and oligodeoxyribonucleotides which hybridise with a nucleotide sequence from the 5' region of the Ki-67 mRNA, i.e. oligoribo- or oligodeoxyribonucleotides which are complementary to the 5' region of the sequence shown in figure 1, preferably to a section of the region from position 197 to 2673 or 2673 to 9962, particularly preferably 197 to 220, have furthermore proved to be particularly active.

The oligonucleotides according to the invention preferably have a chain length of 12 to 66 nucleotides, particularly preferably 17 to 46 and very particularly preferably 22 to 46 nucleotides.

The sequence (SEQ ID NO: 3):

(5'-ACC AGG CGT CTC GTG GGC CAC AT)

is very particularly preferred.

Non-modified oligonucleotides, and in particular non-modified oligoribonucleotides, are subject to nucleolytic degradation to a high degree and therefore have only a low stability and biological half-life. To improve ability to penetrate through membranes and to increase the biological half-life, the bases, sugar residues and/or phosphate residues of the oligonucleotides according to the invention are preferably modified.

Oligonucleotides in which one or more phosphate groups are replaced by phosphothioate, methylphosphonate, phosphoramidate, methylene(methylimino) (MMI) and/or guanidine groups are preferred. The structure of these groups is shown in figure 2. Thiolated oligonucleotides, i.e. oligonucleotides in which phosphate groups are replaced by phosphothioate groups, are particularly preferred. One or more of the phosphate groups of the oligonucleotide can be modified. In the case of partial modification, terminal groups are preferably modified, but oligonucleotides in which all the phosphate groups are modified are most preferred.

Preferred sugar modifications comprise replacement of one or more ribose residues of the oligonucleotide by hexose (figure 2) or by amino acids (peptide nucleic acid, PNA, figure 2).

- 5 Modifications of the bases comprise the use of 5-propinyl-uracyl, 5-propinylcytosine and the tricyclic cytosine analogue phenoxazine.

The synthesis of modified oligonucleotides and further suitable
10 ways of modification are described in the literature (cf., for example, E. Uhlmann, A. Peyman, loc. cit.; M.D. Matteucci, R.W. Wagner, loc. cit.).

The oligonucleotides according to the invention can moreover be
15 protected against degradation by *exo*-nucleases by terminal 3'-3' and/or 5'-5' internucleotide bonds (H. Seliger et al., Nucleosides & Nucleotides 10 (1-3), 469-477 (1991)).

The oligonucleotides according to the invention can furthermore
20 additionally be substituted by groups which promote intracellular uptake, which serve *in vivo* or *in vitro* as reporter groups, and/or groups which, during hybridization of the oligoribonucleotide on the target RNA, attack the same by bonding or cleavage.

25 Examples of groups which promote intracellular uptake are lipophilic residues, such as alkyl residues, for example having 1 to 18 C atoms, cholesteryl or thiocholesteryl groups (E. Uhlmann, A. Peyman, loc. cit.) or conjugates which utilise
30 natural carrier systems, such as e.g. bile acid or peptides for the corresponding receptor (e.g. receptor-mediated endocytosis).

Examples of reporter groups are fluorescent groups (e.g. acridinyl, dansyl or fluoresceinyl groups) or chemiluminescent
35 groups, such as e.g. acridinium ester groups.

- 7 -

start-2-anti	5'-ACC AGG CGT CTC GTG GGC CAC AT
start-2-sense	5'-ATG TGG CCC ACG AGA CGC CTG GT
missense	5'-AGT ACT CAG TAA CGC CTA CGG TAA G

5 Unless stated otherwise, all the oligonucleotides were employed in thiolated form, i.e. one oxygen atom of the phosphoric acid radicals was replaced by a sulphur atom.

10 Multicellular spheroids of the cell line RT-4 (ATCC no.: HTB2) were prepared by the method of Carlsson & Yuhas (J. Carlsson and J.M. Yuhas, Liquid-overlay culture of cellular spheroids, Recent Results in Cancer Research 95; 1-23, 1984). After four days the multicellular spheroids showed a spherical morphology with a pronounced, sharp demarcation. The RT4 multicellular spheroids
15 were then incubated in the presence of 120 μ mol/l of the particular oligonucleotides in culture media at 37°C with 5% CO₂ and the change in the spheroid diameter was measured. The oligonucleotides were introduced into the medium directly after the period of time necessary for formation of the spheroids. On
20 the one hand a sample to which no oligonucleotides were added (control) and on the other hand the missense and sense oligonucleotide samples served as negative controls. Thereafter, the diameter of the multicellular spheroids was measured at intervals of 2 days. Three identical batches were investigated
25 per test and the mean was then obtained. The results are plotted as a graph in figure 3.

An increase in the spheroid diameter to 132% of the starting value was observed in the control, while the addition of the
30 thiolated missense oligonucleotide caused a stop in growth. The addition of the sense oligodeoxynucleotide caused a slight reduction in the spheroid diameter to 90%, while the antisense oligonucleotide led to a rapid decrease in the spheroid diameter down to complete dissolution of the spheroid on the 12th day of
35 incubation.

- 8 -

After co-incubation of the multicellular spheroids with oligonucleotides, these were furthermore tested in respect of their vitality with the aid of fluorescent dyes. The dyes used for this were fluorescein-labelled disodium acetate (FITC-FDA) and propidium iodide (PI). Each multicellular spheroid was incubated with 2 μ l FITC-FDA in a concentration of 1 μ mol/l for 20 minutes and with 10 μ l PI (concentration: 20 μ g/ml) for 10 minutes. Under a fluorescence microscope living cells appear green due to the FITC-FDA staining and dead cells appear red due to the PI staining. A pronounced cytotoxic reaction of the cells investigated in the antisense-treated group was found.

The results show that the antisense oligonucleotide according to the invention is cytotoxic to the tumour cell line tested and causes irreversible cell damage, which leads to death of the cell.

To rule out the solvent alone having an influence on growth, corresponding control experiments were carried out with the solvent (solvent; only the solvent of the oligonucleotides, but not the oligonucleotides themselves, was added), which showed that this influencing parameter was to be ignored (cf. figure 4).

Example 2

Action on the growth of RT4 cells by microinjection

The action of the oligonucleotides mentioned in example 1 on RT4 cells by direct injection of the compounds into the cell was investigated. The oligonucleotides were employed in non-modified (non-thiolated) form for this experiment. By this test, on the one hand the activity of non-modified oligonucleotides is to be demonstrated, and on the other hand non-specific binding of the oligodeoxynucleotides to cell membrane receptors being responsible for the effects described in example 1 is to be ruled out.

- 10 -

- of liquid flowing out per injection as constant as possible for the same injection parameters. Nevertheless, the volume initiated varied from cell to cell, since the injection pressure and therefore the solution to be injected could spread out to a better or worse degree, depending on the region hit. To minimize the effects of cooling and a pH shift of the culture medium on the growth behaviour of the cells, the total injection time per cell culture dish was limited to 15 minutes.
- 10 The results of the test are plotted as a graph in fig. 5. It was found that injection of antisense oligonucleotides and a subsequent incubation time of 22 hours resulted in a loss of adhesion in approx. 70% of the cells. Since only living cells remain adhered to the cover glass, this result is to be equated with death of 70% of the cells. Injection of the sense or missense oligonucleotides led only to a loss of adhesion in 30% of the cells in each case, and sole injection of the solvent (PBS) led to a loss of adhesion in 10% of the cells.

20

Example 3

Action on the growth of J82 cells

- The action of the oligonucleotides on the human bladder tumour cells line J82 was investigated analogously to example 1. The thiolated antisense oligonucleotide in a concentration of 120 $\mu\text{mol/l}$ led to a decrease in the spheroid diameter by 20% after 11 days, while the spheroid diameter of the control increased by about 30% in the same period of time (fig. 6).

- 11 -

SEQUENCE LISTING

(1) GENERAL INFORMATION:

5

(i) APPLICANT:

(A) NAME: Forschungszentrum Borstel
(B) STREET: Parkallee 1-40
(C) CITY: Borstel
(D) State: Schleswig-Holstein
(E) COUNTRY: Germany
(F) POSTAL CODE: D 23845

10

(ii) TITLE OF INVENTION: Antisense-Oligonucleotides for treating proliferating cells

15

(iii) NUMBER OF SEQUENCES: 3

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPA)

20

25

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENZ CHARACTERISTICS:

(A) LENGTH: 12493 base pairs
(B) TYPE: Nucleotid
(C) STRANDEDNESS: dopple strand
(D) TOPOLOGY: linear

30

(ii) MOLECULE TYPE: cDNS

35

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 197..9964

40

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

45	CTACCGGGCG GAGGTGAGCG CGGCGCCGGC TCCTCCTGCG GCGGACTTTG GGTGCGACTT	60
	GACGAGCGGT GGTTCGACAA GTGGCCTTGC GGGCCGGATC GTCCCAGTGG AAGAGTTGTA	120
	AATTGCTTC TGGCCTTCCC CTACGGATTA TACCTGGCCT TCCCCTACGG ATTATACTCA	180
50	ACTTACTGTT TAGAAA ATG TGG CCC ACG AGA CGC CTG GTT ACT ATC AAA	229
	Met Trp Pro Thr Arg Arg Leu Val Thr Ile Lys	
	1 5 10	
55	AGG AGC GGG GTC GAC GGT CCC CAC TTT CCC CTG AGC CTC AGC ACC TGC	277
	Arg Ser Gly Val Asp Gly Pro His Phe Pro Leu Ser Leu Ser Thr Cys	
	15 20 25	
60	TTG TTT GGA AGG GGT ATT GAA TGT GAC ATC CGT ATC CAG CTT CCT GTT	325
	Leu Phe Gly Arg Gly Ile Glu Cys Asp Ile Arg Ile Gln Leu Pro Val	
	30 35 40	
	GTG TCA AAA CAA CAT TGC AAA GTT GAA ATC CAT GAG CAG GAG GCA ATA	373
	Val Ser Lys Gln His Cys Lys Val Glu Ile His Glu Gln Glu Ala Ile	
	45 50 55	

65

- 13 -

	AAC	AAG	GGG	AAG	GGA	AGA	GAC	GTG	GAG	TCT	GTT	CAG	ACT	CCC	AGC	AAG	1189
	Asn	Lys	Gly	Lys	Gly	Arg	Asp	Val	Glu	Ser	Val	Gln	Thr	Pro	Ser	Lys	
					320					325					330		
5	GCT	GTG	GGC	GCC	AGC	TTT	CCT	CTC	TAT	GAG	CCG	GCT	AAA	ATG	AAG	ACC	1237
	Ala	Val	Gly	Ala	Ser	Phe	Pro	Leu	Tyr	Glu	Pro	Ala	Lys	Met	Lys	Thr	
				335					340					345			
10	CCT	GTA	CAA	TAT	TCA	CAG	CAA	CAA	AAT	TCT	CCA	CAA	AAA	CAT	AAG	AAC	1285
	Pro	Val	Gln	Tyr	Ser	Gln	Gln	Gln	Asn	Ser	Pro	Gln	Lys	His	Lys	Asn	
			350					355					360				
15	AAA	GAC	CTG	TAT	ACT	ACT	GGT	AGA	AGA	GAA	TCT	GTG	AAT	CTG	GGT	AAA	1333
	Lys	Asp	Leu	Tyr	Thr	Thr	Gly	Arg	Arg	Glu	Ser	Val	Asn	Leu	Gly	Lys	
		365					370					375					
20	AGT	GAA	GGC	TTC	AAG	GCT	GGT	GAT	AAA	ACT	CTT	ACT	CCC	AGG	AAG	CTT	1381
	Ser	Glu	Gly	Phe	Lys	Ala	Gly	Asp	Lys	Thr	Leu	Thr	Pro	Arg	Lys	Leu	
	380					385					390					395	
	TCA	ACT	AGA	AAT	CGA	ACA	CCA	GCT	AAA	GTT	GAA	GAT	GCA	GCT	GAC	TCT	1429
	Ser	Thr	Arg	Asn	Arg	Thr	Pro	Ala	Lys	Val	Glu	Asp	Ala	Ala	Asp	Ser	
					400					405					410		
25	GCC	ACT	AAG	CCA	GAA	AAT	CTC	TCT	TCC	AAA	ACC	AGA	GGA	AGT	ATT	CCT	1477
	Ala	Thr	Lys	Pro	Glu	Asn	Leu	Ser	Ser	Lys	Thr	Arg	Gly	Ser	Ile	Pro	
				415					420					425			
30	ACA	GAT	GTG	GAA	GTT	CTG	CCT	ACG	GAA	ACT	GAA	ATT	CAC	AAT	GAG	CCA	1525
	Thr	Asp	Val	Glu	Val	Leu	Pro	Thr	Glu	Thr	Glu	Ile	His	Asn	Glu	Pro	
			430					435					440				
35	TTT	TTA	ACT	CTG	TGG	CTC	ACT	CAA	GTT	GAG	AGG	AAG	ATC	CAA	AAG	GAT	1573
	Phe	Leu	Thr	Leu	Trp	Leu	Thr	Gln	Val	Glu	Arg	Lys	Ile	Gln	Lys	Asp	
		445					450					455					
40	TCC	CTC	AGC	AAG	CCT	GAG	AAA	TTG	GGC	ACT	ACA	GCT	GGA	CAG	ATG	TGC	1621
	Ser	Leu	Ser	Lys	Pro	Glu	Lys	Leu	Gly	Thr	Thr	Ala	Gly	Gln	Met	Cys	
	460					465					470					475	
	TCT	GGG	TTA	CCT	GGT	CTT	AGT	TCA	GTT	GAT	ATC	AAC	AAC	TTT	GGT	GAT	1669
	Ser	Gly	Leu	Pro	Gly	Leu	Ser	Ser	Val	Asp	Ile	Asn	Asn	Phe	Gly	Asp	
					480					485					490		
45	TCC	ATT	AAT	GAG	AGT	GAG	GGA	ATA	CCT	TTG	AAA	AGA	AGG	CGT	GTG	TCC	1717
	Ser	Ile	Asn	Glu	Ser	Glu	Gly	Ile	Pro	Leu	Lys	Arg	Arg	Arg	Val	Ser	
				495					500					505			
50	TTT	GGT	GGG	CAC	CTA	AGA	CCT	GAA	CTA	TTT	GAT	GAA	AAC	TTG	CCT	CCT	1765
	Phe	Gly	Gly	His	Leu	Arg	Pro	Glu	Leu	Phe	Asp	Glu	Asn	Leu	Pro	Pro	
			510					515					520				
55	AAT	ACG	CCT	CTC	AAA	AGG	GGA	GAA	GCC	CCA	ACC	AAA	AGA	AAG	TCT	CTG	1813
	Asn	Thr	Pro	Leu	Lys	Arg	Gly	Glu	Ala	Pro	Thr	Lys	Arg	Lys	Ser	Leu	
		525					530					535					
60	GTA	ATG	CAC	ACT	CCA	CCT	GTC	CTG	AAG	AAA	ATC	ATC	AAG	GAA	CAG	CCT	1861
	Val	Met	His	Thr	Pro	Pro	Val	Leu	Lys	Lys	Ile	Ile	Lys	Glu	Gln	Pro	
	540					545					550				555		
	CAA	CCA	TCA	GGA	AAA	CAA	GAG	TCA	GGT	TCA	GAA	ATC	CAT	GTG	GAA	GTG	1909
	Gln	Pro	Ser	Gly	Lys	Gln	Glu	Ser	Gly	Ser	Glu	Ile	His	Val	Glu	Val	
					560					565					570		

65

- 15 -

		CCT	CCC	TTA	AGA	CGG	CAG	TGT	ATT	AGA	GAA	AAT	GGA	AAC	GTA	GCA	AAA	2725
		Pro	Pro	Leu	Arg	Arg	Gln	Cys	Ile	Arg	Glu	Asn	Gly	Asn	Val	Ala	Lys	
				830					835					840				
5		ACG	CCC	AGG	AAC	ACC	TAC	AAA	ATG	ACT	TCT	CTG	GAG	ACA	AAA	ACT	TCA	2773
		Thr	Pro	Arg	Asn	Thr	Tyr	Lys	Met	Thr	Ser	Leu	Glu	Thr	Lys	Thr	Ser	
			845					850					855					
10		GAT	ACT	GAG	ACA	GAG	CCT	TCA	AAA	ACA	GTA	TCC	ACT	GTA	AAC	AGG	TCA	2821
		Asp	Thr	Glu	Thr	Glu	Pro	Ser	Lys	Thr	Val	Ser	Thr	Val	Asn	Arg	Ser	
		860					865					870				875		
15		GGA	AGG	TCT	ACA	GAG	TTC	AGG	AAT	ATA	CAG	AAG	CTA	CCT	GTG	GAA	AGT	2869
		Gly	Arg	Ser	Thr	Glu	Phe	Arg	Asn	Ile	Gln	Lys	Leu	Pro	Val	Glu	Ser	
						880					885					890		
20		AAG	AGT	GAA	GAA	ACA	AAT	ACA	GAA	ATT	GTT	GAG	TGC	ATC	CTA	AAA	AGA	2917
		Lys	Ser	Glu	Glu	Thr	Asn	Thr	Glu	Ile	Val	Glu	Cys	Ile	Leu	Lys	Arg	
					895					900					905			
25		GGT	CAG	AAG	GCA	ACA	CTA	CTA	CAA	CAA	AGG	AGA	GAA	GGA	GAG	ATG	AAG	2965
		Gly	Gln	Lys	Ala	Thr	Leu	Leu	Gln	Gln	Arg	Arg	Glu	Gly	Glu	Met	Lys	
				910					915					920				
30		GAA	ATA	GAA	AGA	CCT	TTT	GAG	ACA	TAT	AAG	GAA	AAT	ATT	GAA	TTA	AAA	3013
		Glu	Ile	Glu	Arg	Pro	Phe	Glu	Thr	Tyr	Lys	Glu	Asn	Ile	Glu	Leu	Lys	
			925					930					935					
35		GAA	AAC	GAT	GAA	AAG	ATG	AAA	GCA	ATG	AAG	AGA	TCA	AGA	ACT	TGG	GGG	3061
		Glu	Asn	Asp	Glu	Lys	Met	Lys	Ala	Met	Lys	Arg	Ser	Arg	Thr	Trp	Gly	
		940					945					950				955		
40		CAG	AAA	TGT	GCA	CCA	ATG	TCT	GAC	CTG	ACA	GAC	CTC	AAG	AGC	TTG	CCT	3109
		Gln	Lys	Cys	Ala	Pro	Met	Ser	Asp	Leu	Thr	Asp	Leu	Lys	Ser	Leu	Pro	
						960				965						970		
45		GAT	ACA	GAA	CTC	ATG	AAA	GAC	ACG	GCA	CGT	GGC	CAG	AAT	CTC	CTC	CAA	3157
		Asp	Thr	Glu	Leu	Met	Lys	Asp	Thr	Ala	Arg	Gly	Gln	Asn	Leu	Leu	Gln	
					975					980					985			
50		ACC	CAA	GAT	CAT	GCC	AAG	GCA	CCA	AAG	AGT	GAG	AAA	GGC	AAA	ATC	ACT	3205
		Thr	Gln	Asp	His	Ala	Lys	Ala	Pro	Lys	Ser	Glu	Lys	Gly	Lys	Ile	Thr	
				990					995					1000				
55		AAA	ATG	CCC	TGC	CAG	TCA	TTA	CAA	CCA	GAA	CCA	ATA	AAC	ACC	CCA	ACA	3253
		Lys	Met	Pro	Cys	Gln	Ser	Leu	Gln	Pro	Glu	Pro	Ile	Asn	Thr	Pro	Thr	
			1005					1010					1015					
60		CAC	ACA	AAA	CAA	CAG	TTG	AAG	GCA	TCC	CTG	GGG	AAA	GTA	GGT	GTG	AAA	3301
		His	Thr	Lys	Gln	Gln	Leu	Lys	Ala	Ser	Leu	Gly	Lys	Val	Gly	Val	Lys	
		1020					1025					1030					1035	
65		GAA	GAG	CTC	CTA	GCA	GTC	GGC	AAG	TTC	ACA	CGG	ACG	TCA	GGG	GAG	ACC	3349
		Glu	Glu	Leu	Leu	Ala	Val	Gly	Lys	Phe	Thr	Arg	Thr	Ser	Gly	Glu	Thr	
						1040					1045					1050		
70		ACG	CAC	ACG	CAC	AGA	GAG	CCA	GCA	GGA	GAT	GGC	AAG	AGC	ATC	AGA	ACG	3397
		Thr	His	Thr	His	Arg	Glu	Pro	Ala	Gly	Asp	Gly	Lys	Ser	Ile	Arg	Thr	
					1055					1060					1065			
75		TTT	AAG	GAG	TCT	CCA	AAG	CAG	ATC	CTG	GAC	CCA	GCA	GCC	CGT	GTA	ACT	3445
		Phe	Lys	Glu	Ser	Pro	Lys	Gln	Ile	Leu	Asp	Pro	Ala	Ala	Arg	Val	Thr	
				1070					1075					1080				

- 16 -

	GGA ATG AAG AAG TGG CCA AGA ACG CCT AAG GAA GAG GCC CAG TCA CTA	3493
	Gly Met Lys Lys Trp Pro Arg Thr Pro Lys Glu Glu Ala Gln Ser Leu	
	1085 1090 1095	
5	GAA GAC CTG GCT GGC TTC AAA GAG CTC TTC CAG ACA CCA GGT CCC TCT	3541
	Glu Asp Leu Ala Gly Phe Lys Glu Leu Phe Gln Thr Pro Gly Pro Ser	
	1100 1105 1110 1115	
10	GAG GAA TCA ATG ACT GAT GAG AAA ACT ACC AAA ATA GCC TGC AAA TCT	3589
	Glu Glu Ser Met Thr Asp Glu Lys Thr Thr Lys Ile Ala Cys Lys Ser	
	1120 1125 1130	
15	CCA CCA CCA GAA TCA GTG GAC ACT CCA ACA AGC ACA AAG CAA TGG CCT	3637
	Pro Pro Pro Glu Ser Val Asp Thr Pro Thr Ser Thr Lys Gln Trp Pro	
	1135 1140 1145	
	AAG AGA AGT CTC AGG AAA GCA GAT GTA GAG GAA GAA TTC TTA GCA CTC	3685
	Lys Arg Ser Leu Arg Lys Ala Asp Val Glu Glu Glu Phe Leu Ala Leu	
	1150 1155 1160	
20	AGG AAA CTA ACA CCA TCA GCA GGG AAA GCC ATG CTT ACG CCC AAA CCA	3733
	Arg Lys Leu Thr Pro Ser Ala Gly Lys Ala Met Leu Thr Pro Lys Pro	
	1165 1170 1175	
25	GCA GGA GGT GAT GAG AAA GAC ATT AAA GCA TTT ATG GGA ACT CCA GTG	3781
	Ala Gly Gly Asp Glu Lys Asp Ile Lys Ala Phe Met Gly Thr Pro Val	
	1180 1185 1190 1195	
30	CAG AAA CTG GAC CTG GCA GGA ACT TTA CCT GGC AGC AAA AGA CAG CTA	3829
	Gln Lys Leu Asp Leu Ala Gly Thr Leu Pro Gly Ser Lys Arg Gln Leu	
	1200 1205 1210	
35	CAG ACT CCT AAG GAA AAG GCC CAG GCT CTA GAA GAC CTG GCT GGC TTT	3877
	Gln Thr Pro Lys Glu Lys Ala Gln Ala Leu Glu Asp Leu Ala Gly Phe	
	1215 1220 1225	
	AAA GAG CTC TTC CAG ACT CCT GGT CAC ACC GAG GAA TTA GTG GCT GCT	3925
	Lys Glu Leu Phe Gln Thr Pro Gly His Thr Glu Glu Leu Val Ala Ala	
	1230 1235 1240	
40	GGT AAA ACC ACT AAA ATA CCC TGC GAC TCT CCA CAG TCA GAC CCA GTG	3973
	Gly Lys Thr Thr Lys Ile Pro Cys Asp Ser Pro Gln Ser Asp Pro Val	
	1245 1250 1255	
45	GAC ACC CCA ACA AGC ACA AAG CAA CGA CCC AAG AGA AGT ATC AGG AAA	4021
	Asp Thr Pro Thr Ser Thr Lys Gln Arg Pro Lys Arg Ser Ile Arg Lys	
	1260 1265 1270 1275	
50	GCA GAT GTA GAG GGA GAA CTC TTA GCG TGC AGG AAT CTA ATG CCA TCA	4069
	Ala Asp Val Glu Gly Glu Leu Leu Ala Cys Arg Asn Leu Met Pro Ser	
	1280 1285 1290	
55	GCA GGC AAA GCC ATG CAC ACG CCT AAA CCA TCA GTA GGT GAA GAG AAA	4117
	Ala Gly Lys Ala Met His Thr Pro Lys Pro Ser Val Gly Glu Glu Lys	
	1295 1300 1305	
	GAC ATC ATC ATA TTT GTG GGA ACT CCA GTG CAG AAA CTG GAC CTG ACA	4165
	Asp Ile Ile Ile Phe Val Gly Thr Pro Val Gln Lys Leu Asp Leu Thr	
	1310 1315 1320	
60	GAG AAC TTA ACC GGC AGC AAG AGA CGG CCA CAA ACT CCT AAG GAA GAG	4213
	Glu Asn Leu Thr Gly Ser Lys Arg Arg Pro Gln Thr Pro Lys Glu Glu	
	1325 1330 1335	
65		

		GAG Glu 2620	AGG Arg	CTC Leu	ACG Thr	CAA Gln	ACA Thr 2625	TCA Ser	GGG Gly	CAA Gln	AGC Ser	ACA Thr 2630	CAC His	ACA Thr	CAC His	AAA Lys	GAA Glu 2635	8101
5		CCA Pro	GCA Ala	AGC Ser	GGT Gly 2640	GAT Asp	GAG Glu	GGC Gly	ATC Ile	AAA Lys	GTA Val 2645	TTG Leu	AAG Lys	CAA Gln	CGT Arg	GCA Ala 2650	AAG Lys	8149
10		AAG Lys	AAA Lys	CCA Pro	AAC Asn 2655	CCA Pro	GTA Val	GAA Glu	GAG Glu	GAA Glu 2660	CCC Pro	AGC Ser	AGG Arg	AGA Arg	AGG Arg 2665	CCA Pro	AGA Arg	8197
15		GCA Ala	CCT Pro	AAG Lys 2670	GAA Glu	AAG Lys	GCC Ala	CAA Gln	CCC Pro 2675	CTG Leu	GAA Glu	GAC Asp	CTG Leu	GCC Ala 2680	GGC Gly	TTC Phe	ACA Thr	8245
20		GAG Glu 2685	CTC Leu	TCT Ser	GAA Glu	ACA Thr	TCA Ser	GGT Gly 2690	CAC His	ACT Thr	CAG Gln	GAA Glu 2695	TCA Ser	CTG Leu	ACT Thr	GCT Ala	GGC Gly	8293
		AAA Lys 2700	GCC Ala	ACT Thr	AAA Lys	ATA Ile	CCC Pro 2705	TGC Cys	GAA Glu	TCT Ser	CCC Pro	CCA Pro 2710	CTA Leu	GAA Glu	GTG Val	GTA Val	GAC Asp 2715	8341
25		ACC Thr	ACA Thr	GCA Ala	AGC Ser	ACA Thr 2720	AAG Lys	AGG Arg	CAT His	CTC Leu	AGG Arg 2725	ACA Thr	CGT Arg	GTG Val	CAG Gln	AAG Lys 2730	GTA Val	8389
30		CAA Gln	GTA Val	AAA Lys	GAA Glu 2735	GAG Glu	CCT Pro	TCA Ser	GCA Ala	GTC Val 2740	AAG Lys	TTC Phe	ACA Thr	CAA Gln	ACA Thr 2745	TCA Ser	GGG Gly	8437
35		GAA Glu	ACC Thr	ACG Thr 2750	GAT Asp	GCA Ala	GAC Asp	AAA Lys	GAA Glu 2755	CCA Pro	GCA Ala	GGT Gly	GAA Glu	GAT Asp 2760	AAA Lys	GGC Gly	ATC Ile	8485
40		AAA Lys 2765	GCA Ala	TTG Leu	AAG Lys	GAA Glu	TCT Ser	GCA Ala 2770	AAA Lys	CAG Gln	ACA Thr	CCG Pro	GCT Ala 2775	CCA Pro	GCA Ala	GCA Ala	AGT Ser	8533
		GTA Val 2780	ACT Thr	GGC Gly	AGC Ser	AGG Arg 2785	AGA Arg	CGG Arg	CCA Pro	AGA Arg	GCA Ala	CCC Pro 2790	AGG Arg	GAA Glu	AGT Ser	GCC Ala	CAA Gln 2795	8581
45		GCC Ala	ATA Ile	GAA Glu	GAC Asp	CTA Leu 2800	GCT Ala	GGC Gly	TTC Phe	AAA Lys	GAC Asp 2805	CCA Pro	GCA Ala	GCA Ala	GGT Gly	CAC His 2810	ACT Thr	8629
50		GAA Glu	GAA Glu	TCA Ser 2815	ATG Met	ACT Thr	GAT Asp	GAC Asp	AAA Lys	ACC Thr 2820	ACT Thr	AAA Lys	ATA Ile	CCC Pro	TGC Cys 2825	AAA Lys	TCA Ser	8677
55		TCA Ser	CCA Pro	GAA Glu 2830	CTA Leu	GAA Glu	GAC Asp	ACC Thr	GCA Ala 2835	ACA Thr	AGC Ser	TCA Ser	AAG Lys	AGA Arg 2840	CGG Arg	CCC Pro	AGG Arg	8725
		ACA Thr 2845	CGT Arg	GCC Ala	CAG Gln	AAA Lys	GTA Val	GAA Glu 2850	GTG Val	AAG Lys	GAG Glu	GAG Glu 2855	CTG Leu	TTA Leu	GCA Ala	GTT Val	GGC Gly	8773
60		AAG Lys 2860	CTC Leu	ACA Thr	CAA Gln	ACC Thr 2865	TCA Ser	GGG Gly	GAG Glu	ACC Thr	ACG Thr 2870	CAC His	ACC Thr	GAC Asp	AAA Lys	GAG Glu	CCG Pro 2875	8821

- 23 -

	GTA	GGT	GAG	GGC	AAA	GGC	ACG	AAA	GCA	TTT	AAG	CAA	CCT	GCA	AAG	CGG	8869
	Val	Gly	Glu	Gly	Lys	Gly	Thr	Lys	Ala	Phe	Lys	Gln	Pro	Ala	Lys	Arg	
					2880					2885					2890		
5	AAC	GTG	GAC	GCA	GAA	GAT	GTA	ATT	GGC	AGC	AGG	AGA	CAG	CCA	AGA	GCA	8917
	Asn	Val	Asp	Ala	Glu	Asp	Val	Ile	Gly	Ser	Arg	Arg	Gln	Pro	Arg	Ala	
				2895					2900						2905		
10	CCT	AAG	GAA	AAG	GCC	CAA	CCC	CTG	GAA	GAC	CTG	GCC	AGC	TTC	CAA	GAG	8965
	Pro	Lys	Glu	Lys	Ala	Gln	Pro	Leu	Glu	Asp	Leu	Ala	Ser	Phe	Gln	Glu	
			2910					2915						2920			
15	CTC	TCT	CAA	ACA	CCA	GGC	CAC	ACT	GAG	GAA	CTG	GCA	AAT	GGT	GCT	GCT	9013
	Leu	Ser	Gln	Thr	Pro	Gly	His	Thr	Glu	Glu	Leu	Ala	Asn	Gly	Ala	Ala	
			2925				2930					2935					
20	GAT	AGC	TTT	ACA	AGC	GCT	CCA	AAG	CAA	ACA	CCT	GAC	AGT	GGA	AAA	CCT	9061
	Asp	Ser	Phe	Thr	Ser	Ala	Pro	Lys	Gln	Thr	Pro	Asp	Ser	Gly	Lys	Pro	
	2940					2945					2950					2955	
25	CTA	AAA	ATA	TCC	AGA	AGA	GTT	CTT	CGG	GCC	CCT	AAA	GTA	GAA	CCC	GTG	9109
	Leu	Lys	Ile	Ser	Arg	Arg	Val	Leu	Arg	Ala	Pro	Lys	Val	Glu	Pro	Val	
					2960					2965					2970		
30	GGA	GAC	GTG	GTA	AGC	ACC	AGA	GAC	CCT	GTA	AAA	TCA	CAA	AGC	AAA	AGC	9157
	Gly	Asp	Val	Val	Ser	Thr	Arg	Asp	Pro	Val	Lys	Ser	Gln	Ser	Lys	Ser	
				2975					2980						2985		
35	AAC	ACT	TCC	CTG	CCC	CCA	CTG	CCC	TTC	AAG	AGG	GGA	GGT	GGC	AAA	GAT	9205
	Asn	Thr	Ser	Leu	Pro	Pro	Leu	Pro	Phe	Lys	Arg	Gly	Gly	Gly	Lys	Asp	
			2990				2995						3000				
40	GGA	AGC	GTC	ACG	GGA	ACC	AAG	AGG	CTG	CGC	TGC	ATG	CCA	GCA	CCA	GAG	9253
	Gly	Ser	Val	Thr	Gly	Thr	Lys	Arg	Leu	Arg	Cys	Met	Pro	Ala	Pro	Glu	
		3005					3010					3015					
45	GAA	ATT	GTG	GAG	GAG	CTG	CCA	GCC	AGC	AAG	AAG	CAG	AGG	GTT	GCT	CCC	9301
	Glu	Ile	Val	Glu	Glu	Leu	Pro	Ala	Ser	Lys	Lys	Gln	Arg	Val	Ala	Pro	
	3020					3025					3030					3035	
50	AGG	GCA	AGA	GGC	AAA	TCA	TCC	GAA	CCC	GTG	GTC	ATC	ATG	AAG	AGA	AGT	9349
	Arg	Ala	Arg	Gly	Lys	Ser	Ser	Glu	Pro	Val	Val	Ile	Met	Lys	Arg	Ser	
				3040						3045					3050		
55	TTG	AGG	ACT	TCT	GCA	AAA	AGA	ATT	GAA	CCT	GCG	GAA	GAG	CTG	AAC	AGC	9397
	Leu	Arg	Thr	Ser	Ala	Lys	Arg	Ile	Glu	Pro	Ala	Glu	Glu	Leu	Asn	Ser	
				3055					3060						3065		
60	AAC	GAC	ATG	AAA	ACC	AAC	AAA	GAG	GAA	CAC	AAA	TTA	CAA	GAC	TCG	GTC	9445
	Asn	Asp	Met	Lys	Thr	Asn	Lys	Glu	Glu	His	Lys	Leu	Gln	Asp	Ser	Val	
			3070					3075					3080				
65	CCT	GAA	AAT	AAG	GGA	ATA	TCC	CTG	CGC	TCC	AGA	CGC	CAA	GAT	AAG	ACT	9493
	Pro	Glu	Asn	Lys	Gly	Ile	Ser	Leu	Arg	Ser	Arg	Arg	Gln	Asp	Lys	Thr	
		3085					3090					3095					
70	GAG	GCA	GAA	CAG	CAA	ATA	ACT	GAG	GTC	TTT	GTA	TTA	GCA	GAA	AGA	ATA	9541
	Glu	Ala	Glu	Gln	Gln	Ile	Thr	Glu	Val	Phe	Val	Leu	Ala	Glu	Arg	Ile	
	3100					3105					3110					3115	
75	GAA	ATA	AAC	AGA	AAT	GAA	AAG	AAG	CCC	ATG	AAG	ACC	TCC	CCA	GAG	ATG	9589
	Glu	Ile	Asn	Arg	Asn	Glu	Lys	Lys	Pro	Met	Lys	Thr	Ser	Pro	Glu	Met	
				3120						3125					3130		

65

- 25 -

GCCTCCGAAA TCTCCTTTGA AGCCCAGACA TCTTTCTCCA GCTTCAGACT TGTAGATATA 10994
 ACTCGTTCAT CTTCAATTTAC TTTCCACTTT GCCCCCTGTC CTCTCTGTGT TCCCCAAATC 11054
 5 AGAGAAATAGC CCGCCATCCC CCAGATCACC TGTCTGGATT CCTCCCCATT CACCCACCTT 11114
 GCCAGGTGCA GGTGAGGATG GTGCACCAGA CAGGGTAGCT GTCCCCCAA ATGTGCCCTG 11174
 10 TGGCGGCAGT GCCCTGTCTC CACGTTTGTT TCCCCAGTGT CTGGCGGGGA GCCAGGTGAC 11234
 ATCATAAATA CTTGCTGAAT GAATGCAGAA ATCAGCGGTA CTGACTTGTA CTATATTGGC 11294
 TGCCATGATA GGGTTCTCAC AGCGTCATCC ATGATCGTAA GGGAGAATGA CATTCTGCTT 11354
 15 GAGGGAGGGA ATAGAAAGGG GCAGGGAGGG GACATCTGAG GGCTTCACAG GGCTGCAAAG 11414
 GGTACAGGGA TTGCACCAGG GCAGAACAGG GGAGGGTGTT CAAGGAAGAG TGGCTCTTAG 11474
 CAGAGGCACT TTGGAAGGTG TGAGGCATAA ATGCTTCCTT CTACGTAGGC CAACCTCAAA 11534
 20 ACTTTCAGTA GGAATGTTGC TATGATCAAG TTGTTCTAAC ACTTTAGACT TAGTAGTAAT 11594
 TATGAACCTC ACATAGAAAA ATTTCATCCA GCCATATGCC TGTGGAGTGG AATATTCTGT 11654
 25 TTAGTAGAAA AATCCTTTAG AGTTCAGCTC TAACCAGAAA TCTTGCTGAA GTATGTCAGC 11714
 ACCTTTTCTC ACCCTGGTAA GTACAGTATT TCAAGAGCAC GCTAAGGGTG GTTTTCATTT 11774
 TACAGGGCTG TTGATGATGG GTTAAAAATG TTCATTTAAG GGCTACCCCC GTGTTTAATA 11834
 30 GATGAACACC ACTTCTACAC AACCTCCTT GGTACTGGGG GAGGGAGAGA TCTGACAAAT 11894
 ACTGCCCCATT CCCCTAGGCT GACTGGATTT GAGAACAAAT ACCCACCCTT TTCCACCATG 11954
 35 GTATGGTAAC TTCTCTGAGC TTCAGTTTCC AAGTGAATTT CCATGTAATA GGACATTCCC 12014
 ATTAAATACA AGCTGTTTTT ACTTTTTCGC CTCCCAGGGC CTGTGCGATC TGGTCCCCCA 12074
 GCCTCTCTTG GGCTTTCTTA CACTAACTCT GTACCTACCA TCTCCTGCCT CCCTTAGGCA 12134
 40 GGCACCTCCA ACCACCACAC ACTCCCTGCT GTTTTCCCTG CCTGGAACTT TCCCACCAGC 12194
 CCCACCAAGA TCATTTTCATC CAGTCCTGAG CTCAGCTTAA GGGAGGCTTC TTGCCTGTGG 12254
 45 GTTCCCTCAC CCCCATGCCT GTCCTCCAGG CTGGGGCAGG TTCTTAGTTT GCCTGGAATT 12314
 GTTCTGTACC TCTTTGTAGC ACGTAGTGTT GTGAAACTAA GCCACTAATT GAGTTTCTGG 12374
 CTCCCCTCCT GGGGTTGTAA GTTTTGTTCA TTCATGAGGG CCGACTGTAT TTCCTGGTTA 12434
 50 CTGTATCCCA GTGACCAGCC ACAGGAGATG TCCAATAAAG TATGTGATGA AATGGTCTT 12493

(2) INFORMATION FOR SEQ ID NO: 2:

- 55 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 3256 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear
 60 (ii) MOLECULE TYPE: Protein
 (xi) SEQUENCE DISCRIPTION: SEQ ID NO: 2:

65 Met Trp Pro Thr Arg Arg Leu Val Thr Ile Lys Arg Ser Gly Val Asp
 1 5 10 15

- 27 -

	Gln	Gln	Gln	Asn	Ser	Pro	Gln	Lys	His	Lys	Asn	Lys	Asp	Leu	Tyr	Thr	
			355					360					365				
5	Thr	Gly	Arg	Arg	Glu	Ser	Val	Asn	Leu	Gly	Lys	Ser	Glu	Gly	Phe	Lys	
		370					375					380					
	Ala	Gly	Asp	Lys	Thr	Leu	Thr	Pro	Arg	Lys	Leu	Ser	Thr	Arg	Asn	Arg	
	385					390					395					400	
10	Thr	Pro	Ala	Lys	Val	Glu	Asp	Ala	Ala	Asp	Ser	Ala	Thr	Lys	Pro	Glu	
					405					410					415		
	Asn	Leu	Ser	Ser	Lys	Thr	Arg	Gly	Ser	Ile	Pro	Thr	Asp	Val	Glu	Val	
15				420					425					430			
	Leu	Pro	Thr	Glu	Thr	Glu	Ile	His	Asn	Glu	Pro	Phe	Leu	Thr	Leu	Trp	
			435					440					445				
20	Leu	Thr	Gln	Val	Glu	Arg	Lys	Ile	Gln	Lys	Asp	Ser	Leu	Ser	Lys	Pro	
		450					455					460					
	Glu	Lys	Leu	Gly	Thr	Thr	Ala	Gly	Gln	Met	Cys	Ser	Gly	Leu	Pro	Gly	
	465					470					475					480	
25	Leu	Ser	Ser	Val	Asp	Ile	Asn	Asn	Phe	Gly	Asp	Ser	Ile	Asn	Glu	Ser	
					485					490					495		
	Glu	Gly	Ile	Pro	Leu	Lys	Arg	Arg	Arg	Val	Ser	Phe	Gly	Gly	His	Leu	
30				500					505					510			
	Arg	Pro	Glu	Leu	Phe	Asp	Glu	Asn	Leu	Pro	Pro	Asn	Thr	Pro	Leu	Lys	
			515					520					525				
35	Arg	Gly	Glu	Ala	Pro	Thr	Lys	Arg	Lys	Ser	Leu	Val	Met	His	Thr	Pro	
		530					535					540					
	Pro	Val	Leu	Lys	Lys	Ile	Ile	Lys	Glu	Gln	Pro	Gln	Pro	Ser	Gly	Lys	
	545					550					555					560	
40	Gln	Glu	Ser	Gly	Ser	Glu	Ile	His	Val	Glu	Val	Lys	Ala	Gln	Ser	Leu	
					565					570					575		
	Val	Ile	Ser	Pro	Pro	Ala	Pro	Ser	Pro	Arg	Lys	Thr	Pro	Val	Ala	Ser	
45				580					585					590			
	Asp	Gln	Arg	Arg	Arg	Ser	Cys	Lys	Thr	Ala	Pro	Ala	Ser	Ser	Ser	Lys	
			595					600					605				
50	Ser	Gln	Thr	Glu	Val	Pro	Lys	Arg	Gly	Gly	Glu	Arg	Val	Ala	Thr	Cys	
		610					615					620					
	Leu	Gln	Lys	Arg	Val	Ser	Ile	Ser	Arg	Ser	Gln	His	Asp	Ile	Leu	Gln	
	625					630					635					640	
55	Met	Ile	Cys	Ser	Lys	Arg	Arg	Ser	Gly	Ala	Ser	Glu	Ala	Asn	Leu	Ile	
					645					650					655		
	Val	Ala	Lys	Ser	Trp	Ala	Asp	Val	Val	Lys	Leu	Gly	Ala	Lys	Gln	Thr	
60				660					665					670			
	Gln	Thr	Lys	Val	Ile	Lys	His	Gly	Pro	Gln	Arg	Ser	Met	Asn	Lys	Arg	
			675					680					685				
65	Gln	Arg	Arg	Pro	Ala	Thr	Pro	Lys	Lys	Pro	Val	Gly	Glu	Val	His	Ser	
		690					695					700					

- 2 -

8. Use according to anyone of claims 1 to 7, **characterized in that** the oligoribo- or oligodeoxyribonucleotide has a terminal 3'-3' and/or 5'-5' internucleotide linkage.
9. Medicament, **characterized by** a content of an oligoribo- and/or oligodeoxyribonucleotide which is capable of hybridizing with the mRNA which codes for the cell cycle-associated protein Ki-67, or of a physiologically acceptable salt thereof, in addition to conventional carrier substances, auxiliaries and/or additives, wherein the amount of oligonucleotide is adjusted such that an administration of 0.001 to 100 mg/kg of body weight is achieved.
10. Use according to anyone of claims 1 to 8 for treatment of tumours, autoimmune diseases, cicatrization, inflammations, allergies, rheumatic diseases and rejection reactions following transplantations.
11. Process for the preparation of a medicament for destroying proliferating cells, **characterized by** the use of oligoribo- or oligodeoxyribonucleotides which are capable of hybridizing with the mRNA which codes for the protein Ki-67, or of a physiologically acceptable salt thereof.
12. Process according to claim 11 for the preparation of a medicament for treatment of tumours, autoimmune diseases, cicatrization, inflammations, allergies, rheumatic diseases or rejection reactions following transplantations.
13. Process according to claim 11 or 12, comprising combining of an oligoribo- or oligodeoxyribonucleotide which is capable of hybridizing with the mRNA which codes for the protein Ki-67 with conventional carrier substances, auxiliaries and/or additives.

Abstract

The invention relates to oligoribo- and oligodeoxyribonucleotides which are suitable for treating pathological conditions accompanied by increased cell proliferation. The oligoribo- and oligodeoxyribonucleotides are characterized in that they are able to hybridise with the mRNA which codes for the cell cycle-associated protein Ki-67.

[illegible]

Figure 1
(continued)

TGTAAATATTCACAGAGTCTTTCGGGGGCTAAAGTACAGCTTGGGAGAGCTGT 3120
L K E E R F U L R A V K V S E V G D V V 3273

AAAGCCAGAGAGCTCTTAAATACAGAAAGCAAAAGCAATCTTCTGCTGGGCTCTGG 3180
S T K U D V F E G G D K S N T D L E P L Y 3293

CTTCAAGAGGAGCTTGGGAAAGATGAGAGCTGAGGAGAGCTAAGAGGCTGGCTCAT 3240
F X R G G G Y D G E V T G T S R L R C M 3023

[-----] PARTIAL NUCLEAR TARGETING SEQUENCE [-----]
GCGAGAGAGAGAGCTTGGGAGAGCTTGGGAGAGAGAGAGAGAGAGAGAGAGAGAG 3300
P A P K Y E V E S L P A S K R G R V A P 3025

[-----]
GAGGAG 3360
P A R G E D S E P V V I N F R S L N T E 3023

[-----] ATT/UTR-BINDING MOBILE A (Y-LOOP)
TGCAG 3420
A F R C E P A S E L M S M D N F T M K E 3073

GAG 3480
S E Y I D D S V P S M F C T S L R E A R 3093

END OF THE LARGE EXON (1) [-----]
GAG 3540
Q D K T X A E C Q I T E N V P U L A S R C 3113

AG 3600
E I R R N E Y K P M Y T S F S M D I C N 3123

TTGAG 3660
P D D G A R K F P F R P V E E F R C 3133

[-----] PARTIAL NUCLEAR TARGETING SEQUENCE [-----]
CTTCAAG 3720
L R S A R Q N E S D Q P Y V A E S D G G 3173

GAG 3780
Q F D A K V L M Q M Q F G Y G E A G N S 3193

AG 3840
D E M C I R S R K T J S G P A A E T L T 3213

GAG 3900
S K S V Q R V T R S V F R C A E F T F K K 3233

GAG 3960
A E D N V C V F K I T T R S R R D S E P 3253

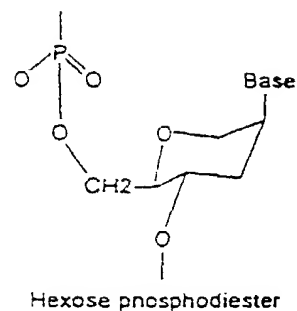
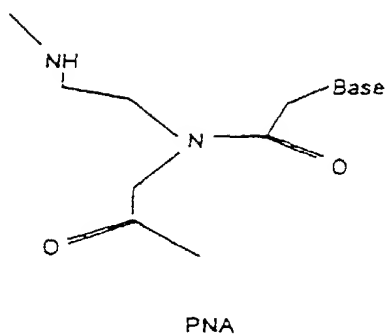
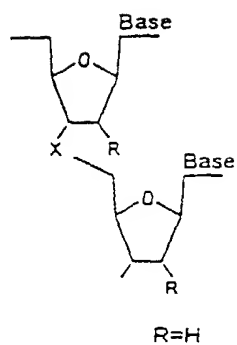
TATTCAG 4020
L 3273

AG 4080
AG 4140
CTGCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 4200
CAAGGTTTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 4260
CTTCAAG 4320
CTTCAAG 4380
CTTCAAG 4440
CAATGGGCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 4500
CTTCAAG 4560
GAG 4620
GCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 4680
CAATCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 4740
CTTCAAG 4800
AGCTTATCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 4860
ATCATCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 4920
GCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 4980
GACTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 5040
CTTCAAG 5100
GATTCAG 5160
CAAAATCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 5220
GGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 5280
TGTACTATCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 5340
ATGAGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 5400
ACAAGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 5460
AGAGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 5520
AGGCACTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 5580
CACTTATCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 5640
CTTCAAG 5700
TGAAG 5760
GCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 5820
GCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 5880
GAG 5940
GATTCAG 6000
AATAG 6060
GCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 6120
GCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 6180
AGCTTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGGCTCTGGG 6240
CTTCAAG 6300
CTTCAAG 6360
CTTCAAG 6420
AATAG 6480
GATTCAG 6540
ATGAG 6600

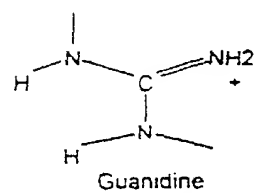
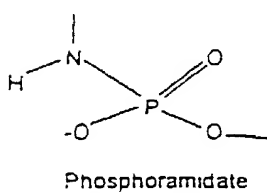
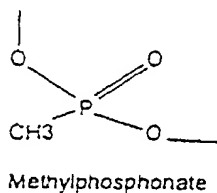
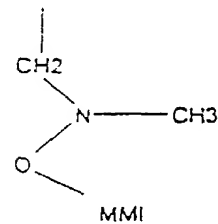
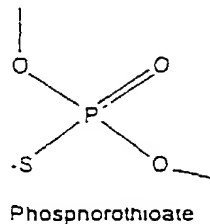
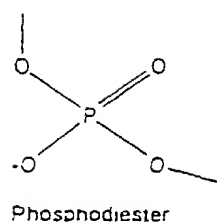
4/6

Figure 2

Structure of sugar- and phosphate-modified oligonucleotides



X=



5/6

Figure 3

Influence of oligonucleotides on RT4 cells.

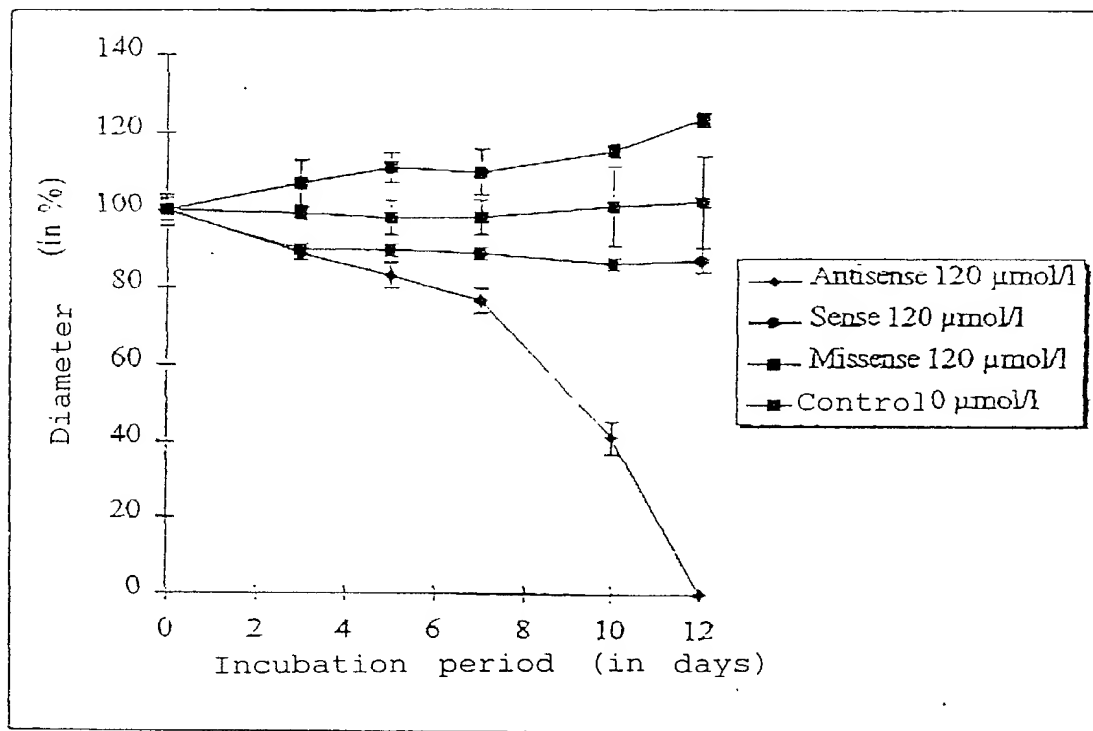


Figure 4

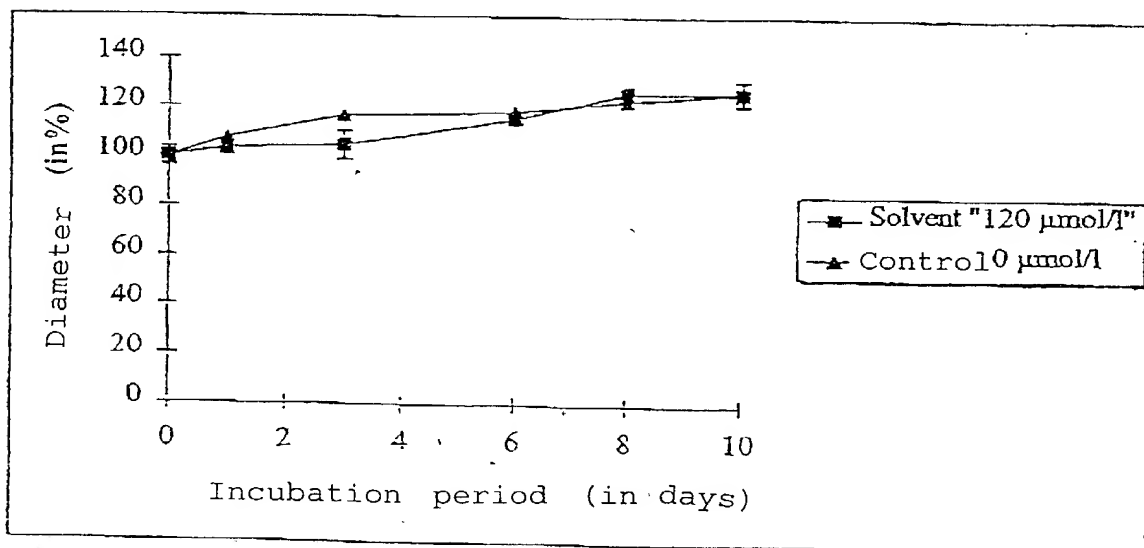
Influence of the solvent on RT4 cells
(negative control)

Figure 5

Influence of oligonucleotides on RT4 cells by microinjection

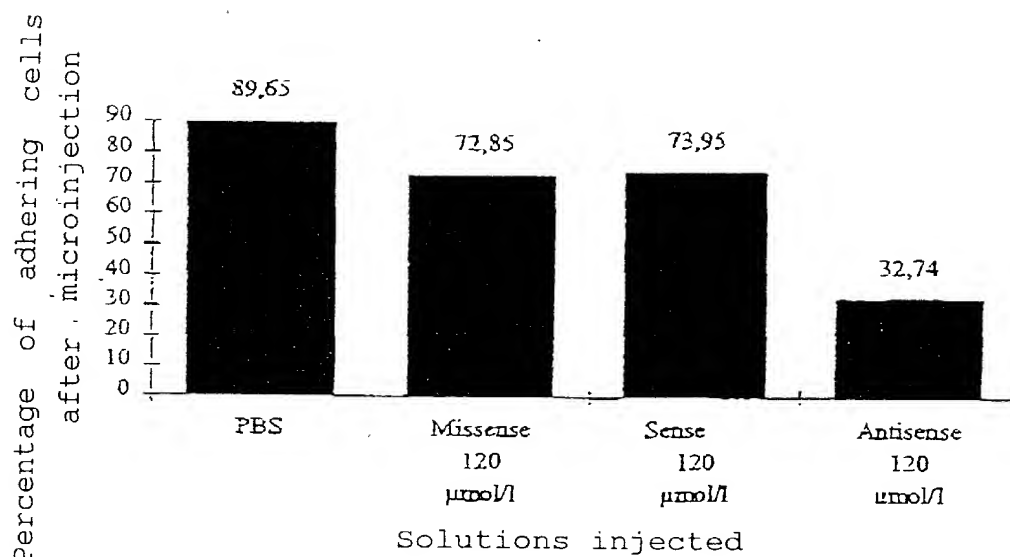
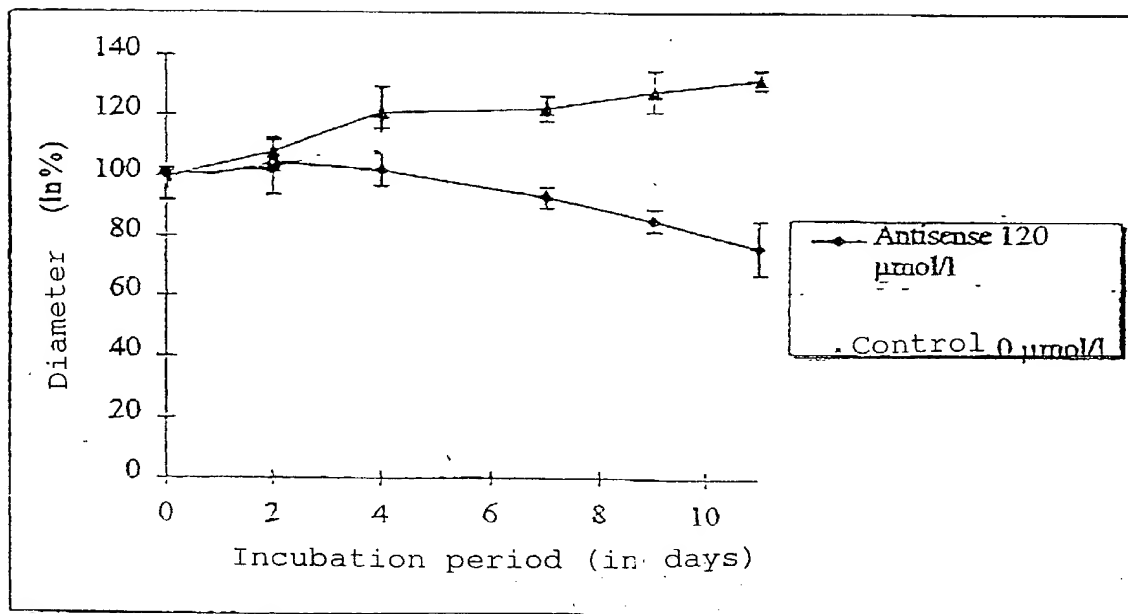


Figure 6

Influence of oligonucleotides on J82 cells



22/02/2001 17:00

+49-40-89965488

UEXKOLL & STOLBERG 0405 022251105

+49+4537188724 S.04

**DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION IN THE
UNITED STATES PATENT AND TRADEMARK OFFICE**

() Declaration Submitted with Initial Filing or (X) Declaration Submitted after Initial Filing (surcharge 37 CFR 1.16 (c) required)

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the INVENTION ENTITLED "ANTISENSE OLIGONUCLEOTIDES FOR TREATING PROLIFERATING CELLS", the specification of which was filed on November 21, 2000 as Attorney Docket No. 661-50203, which is a U.S. National Phase application of PCT International Application No. PCT/EP99/03451.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 including for continuation-in-part application, material information which becomes available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a) -(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international Application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)			Priority Claimed	Certified Copy Attached?
Number	Country	Foreign Filing Date (MM/DD/YYYY)	Yes	No
PCT/EP99/03451		May 20, 1999	Yes	
198 22 954.2	DE	May 22, 1998	Yes	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the registered practitioners represented by Customer No.: 20736 to prosecute this application and transact all business in the U.S. Patent and Trademark Office in connection therewith. Direct all correspondence to Farkas & Manelli, PLLC at Customer No.: 20736.

1. INVENTOR'S SIGNATURE: 1.00 H-D Flad Date 20/02/01
 Inventor's Name (typed) Hans-Dieter Flad Germany
 First Middle Initial Family Name Country of Citizenship
 Residence (City) Borstel DEX Germany
 Post Office Address (Include Zip Code) Parkallee 1, D-23843, Borstel, Germany

2. INVENTOR'S SIGNATURE: 2. J. P. Gerdes Date 20/02/01
 Inventor's Name (typed) Johannes Gerdes Germany
 First Middle Initial Family Name Country of Citizenship
 Residence (City) Feldhorst DEX Germany
 Post Office Address (Include Zip Code) Steinfeld 79, D-23858, Feldhorst, Germany

3. INVENTOR'S SIGNATURE: 3. A. Behle Date 20/2/01
 Inventor's Name (typed) Andreas Behle Germany
 First Middle Initial Family Name Country of Citizenship
 Residence (City) Groß Grönau DEX Germany
 Post Office Address (Include Zip Code) Fasanenring 2, D-23627, Groß Grönau, Germany

4. INVENTOR'S SIGNATURE: _____ Date _____
 Inventor's Name (typed) Irina Deinert Germany
 First Middle Initial Family Name Country of Citizenship
 Residence (City) Lübeck DEX Germany
 Post Office Address (Include Zip Code) Ottomweg 12, D-23560, Lübeck, Germany

22/02/2001 17:00

+49-40-89965488

UEXKOLL&STOLBERG

T43T43J7188724 S.05

DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION IN THE
UNITED STATES PATENT AND TRADEMARK OFFICE

1005 89965488 Declaration Submitted with Initial Filing or [X] Declaration Submitted after Initial Filing (surcharge 37 C.F.R. 1.16 (c) required)

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the INVENTION ENTITLED
"ANTISENSE OLIGONUCLEOTIDES FOR TREATING PROLIFERATING CELLS", the specification of which was filed on
November 21, 2000 as Attorney Docket No. 661-50303, which is a U.S. National Phase application of PCT (International Application
No. PCT/EP99/03451).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 including for continuation-in-part applications, material information which becomes available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a) -(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT (International Application) which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)			Priority Claimed	Certified Copy Attached
Number	Country	Foreign Filing Date (MM/DD/YYYY)	Yes	No
PCT/EP99/03451		May 20, 1999	Yes	
198 22 954.2	DE	May 22, 1998	Yes	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the registered practitioners represented by Customer No.: 20736 to prosecute this application and transact all business in the U.S. Patent and Trademark Office in connection therewith. Direct all correspondence to Farkas & MaueLL, PLLC at Customer No.: 20736.

1. INVENTOR'S SIGNATURE: _____ Date _____
 Inventor's Name (typed) Hans-Dieter Flad Germany
 First Middle Initial Family Name Country of Citizenship
 Residence (City) Borsfel (State) Germany
 Post Office Address (Include Zip Code) Parkallee 1, D-23845, Borsfel, Germany

2. INVENTOR'S SIGNATURE: _____ Date _____
 Inventor's Name (typed) Johannes Geroes Germany
 First Middle Initial Family Name Country of Citizenship
 Residence (City) Feldhorst (State) Germany
 Post Office Address (Include Zip Code) Sternfeld 79, D-27555, Feldhorst, Germany

3. INVENTOR'S SIGNATURE: _____ Date _____
 Inventor's Name (typed) Andreas Böhle Germany
 First Middle Initial Family Name Country of Citizenship
 Residence (City) Groß Grönau (State) Germany
 Post Office Address (Include Zip Code) Fasanengraben 2, D-23627, Groß Grönau, Germany

4. INVENTOR'S SIGNATURE: H. O. R. - D. A. Date 20.02.2001
 Inventor's Name (typed) Inga Enchen-Deinert Germany
 First Middle Initial Family Name Country of Citizenship
 Residence (City) Lübbers Steinburg (State) Germany
 Post Office Address (Include Zip Code) Postfach 17, D-22560, Lübbers, Germany
Reichsmaas 43, D-22964, Steinburg **DE**